REMARKS

Reconsideration of the present application is respectfully requested. By the present amendment all of the pending claims were canceled and replaced by a new set of claims 27-39.[1] Concordance of the new and old claims is as follows:

Old Claim	New Claim
1	27
9	28
11	29
12	30
13	31
15	32
20	33
21	34
22	35
23	36
24	37
25	38
26	39

[1]It is respectfully submitted that Claim 1 of the application was not canceled before the present amendment. There was no submission made in the present application on May 29, 2001. The Examiner appears to have acted on a paper not intended for the present application.

In the Office Action of October 12, 2000, the claims were rejected under 35 USC §112, 1st paragraph as lacking enablement. The Examiner asked for evidence that the oral/enteral tolerance approach would work for various autoimmune conditions.

First, one of the patents cited in Applicants' submission mailed July 5, 2000 is a patent issued based on the same application: U.S. Patent 5,869,054 (Tab 1) is based on Ser. No. 454,832, a continuation of the present application and claims a method for treating multiple sclerosis using MBP or fragments or analogs thereof. This patent is evidence that another Examiner considered the subject matter of the claims of this patent enabled.

Second, a number of the other patents issued to Applicants and co-workers show that the treatment claimed in the present application worked as disclosed in the present application. The fact that these patents may have been issued on different applications does not prevent them from fulfilling the purpose for which they were offered in evidence: they were offered to show that the same type of experiments as described in the present application, namely use of oral/enteral tolerance in models of autoimmune disease resulted in abatement or suppression of autoimmune responses in many different animal models. In other words, the subsequent applications demonstrate that the present oral/enteral administration of an autoantigen before (or after) disease induction results in suppression of the autoimmune-like response in these models of different diseases. The Examiner had

raised an issue with respect to the adequacy of the teaching of the present specification for practicing the claimed broad methods. The patents cited earlier show no evidence that contradicts the teachings of the present application or that calls them into question. They should therefore be considered for what they are worth and for the purpose for which they were submitted. They are similar to experiments conducted and presented in a Rule 132 declaration. Full copies of these patents are submitted with the present response for the Examiner's convenience.

5,869,093 (Tab 2) was issued on a C-I-P of the present application and contains all of the Examples of the present application. The additional examples, Examples 17-24 at cols 23-27, are directed to abatement of an autoimmune response in another model of rheumatoid arthritis (collagen-induced arthritis, Examples 18 and 19) or to the same adoptive transfer experiments (Example 20) as the present Example 10 to show again that suppression by oral tolerance is active suppression, and does not depend on direct encounter between the antigen and the activated T cell that recognizes it. This simply duplicates the methods taught in the present application and therefore supporting the present application.

Similarly, U.S. Patents 5,858,968 (which employs oral tolerance in a model of Type 1 diabetes) and 5,961,977 (which employs oral tolerance in a model of uveoretinitis) are probative of enablement of the presently claimed invention because the experiments therein were performed and worked as the inventors had broadly said they would in the present application. Copies of these two patents are

attached for the Examiner's convenience (Tabs 3 and 4).

As additional evidence of enablement in the present application, applicants point to the following, and attach evidentiary references in support.

The present inventors discovered first a probable mechanism that would be mobilized by oral administration of autoantigen (see present Example 4 and Example 6) and then confirmed this mechanism (see present Example 10). This discovery permitted them to extrapolate to many diseases.

Example 4 shows that suppression could be induced if antigen was administered after disease induction. This was important because human beings are already sensitized to autoantigens.[2]

Example 6 shows that oral administration of a nonencephalitogenic fragment of MBP nevertheless suppressed the autoimmune-like response in EAE. The only explanation for this phenomenon was that some type of active suppression mechanism was triggered, one which did not require administration of the very antigen that induced the disease and one that did not depend on direct encounter between activated T cell and the antigen which it recognizes. Example 6 shows that this phenomenon was independent of the particular autoimmune disease since the rats had not been exposed to MBP prior to being fed the nonencephalitogenic fragment. Consequently, it was not possible for the rats' immune system to "know" that the fed fragment was part of an autoantigen. Nor could the immune system of the healthy

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[2] See more on Example 4 below.

rats "know" which model disease would be induced.

Since it is shown from Example 6 that the fed antigen need not be the same as the disease-inducing antigen,the generality of this therapeutic approach is already established. (This, incidentally, does not occur in anergy, which is the subject of Tisch *et al.*)

Example 10, shows adoptive transfer of suppression. It shows that it is not necessary for the antigen to encounter the treated subject at all. It is sufficient for the T cells of the fed animal (which is not immunized) to be introduced into the diseased animal, where they achieve suppression of the autoimmune-like response. This supports the generality of the oral tolerance phenomenon discovered by the present inventors. (Anergy, the subject of Tisch et al, cannot be adoptively transferred. This is precisely why Tisch expresses all of these reservations for anergy-based treatment. These are not applicable to oral tolerization which triggers active suppression, not anergy.)

But there is also additional, extraneous, evidence that supports the generality of the present invention. In 1981-84, well prior to the earliest date to which the present application is entitled, a group of scientists led by Irun R. Cohen discovered that autoimmune diseases can be transferred from a diseased animal to a healthy animal by transfer of a specific set of T cells that mediate the disease. This was shown for EAE in 1981 (Ben-Nun *et al*, Tab 5) for autoimmune thyroiditis in 1983 (Maron *et al*, Tab 6) and for autoimmune arthritis in 1982 (Holoshitz *et al.*, Tab 7). In

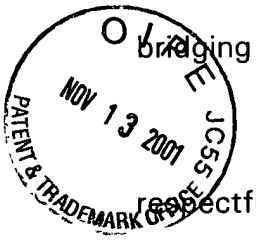
the same series of publications, these authors showed that suppression of the disease-mediating T cells would suppress the disease regardless of whether it was an organ-specific disease like autoimmune thyroiditis or a tissue-specific disease like EAE or autoimmune arthritis. The only requirement of these authors was that the disease should be T cell mediated.

The present inventors extended these findings by showing that one can suppress the harmful T cells by feeding antigen before or after autoimmunity is triggered, by feeding the same antigen as is used to induce the disease, or another tissue-specific antigen, and by feeding antigen in two different and disparate disease models, EAE and adjuvant arthritis. Adjuvant arthritis is triggered by Mt, which although not technically an autoantigen, it acts as one. See Van Eden, W. et al, 1985, PNAS (USA), 82:5117-5120 (Tab 8).

The fact that Example 4 of the present application administers oral antigen at days +2, +5 and +7 does not detract from its importance as a post-immunization experiment. The autoimmune-like response begins on immunization. It takes several days for the *clinical* symptoms to appear but the *autoimmune* response is triggered immediately. Consequently, Example 4 shows that an ongoing autoimmune response is suppressed, and the Examiner's concerns have been addressed.

Lastly there have been no reports of oral tolerance causing any adverse side effects in various clinical trials that have been conducted. For example, Barnett

et al, 1998 (Tab 9) states that there were no side effects not only in the oral tolerance trial which Barnett describes but also in other such clinical trials (see paragraph bridging pp. 296-297).



Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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